

Receipt date: 01/30/2009

Doc code: IDS

Doc description: Information Disclosure Statement (IDS) Filed

10524963 - GAI: 1614

Approved for use through 01/31/2009. OMB 0651-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

|   |                        |                     |            |  |
|---|------------------------|---------------------|------------|--|
| <b>INFORMATION DISCLOSURE<br/>STATEMENT BY APPLICANT</b><br>( Not for submission under 37 CFR 1.99) | Application Number     |                     | 10524963   |  |
|   | Filing Date            |                     | 2005-02-18 |  |
|   | First Named Inventor   | David William Tonge |            |  |
|   | Art Unit               | 1614                |            |  |
|   | Examiner Name          | Leslie A. Royds     |            |  |
|   | Attorney Docket Number | 100815-1P US        |            |  |

| U.S.PATENTS       |         |               |                        |            |   |  | Remove |
|-------------------|---------|---------------|------------------------|------------|---|--|--------|
| Examiner Initial* | Cite No | Patent Number | Kind Code <sup>1</sup> | Issue Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |        |
|                   | 1       |               |                        |            |   |  |        |

If you wish to add additional U.S. Patent citation information please click the Add button.

Add

| U.S.PATENT APPLICATION PUBLICATIONS |         |                    |                        |                  |   |  | Remove |
|-------------------------------------|---------|--------------------|------------------------|------------------|---|--|--------|
| Examiner Initial*                   | Cite No | Publication Number | Kind Code <sup>1</sup> | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |        |
|                                     | 1       |                    |                        |                  |   |  |        |

If you wish to add additional U.S. Published Application citation information please click the Add button.

Add

| FOREIGN PATENT DOCUMENTS |         |                                      |                           |                        |                  |   |  | Remove                   |
|--------------------------|---------|--------------------------------------|---------------------------|------------------------|------------------|---|--|--------------------------|
| Examiner Initial*        | Cite No | Foreign Document Number <sup>3</sup> | Country Code <sup>2</sup> | Kind Code <sup>4</sup> | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear | T <sup>5</sup>           |
|                          | 1       |                                      |                           |                        |                  |   |  | <input type="checkbox"/> |

If you wish to add additional Foreign Patent Document citation information please click the Add button

Add

| NON-PATENT LITERATURE DOCUMENTS |         |   |                | Remove |
|---------------------------------|---------|---|----------------|--------|
| Examiner Initials*              | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T <sup>5</sup> |        |
|                                 |         |   |                |        |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /LAR/ (05/14/2009)

/Leslie A. Royds/ (05/14/2009)

|   |                        |                     |            |                      |
|---|------------------------|---------------------|------------|----------------------|
| <b>Receipt date: 01/30/2009</b><br><br><b>INFORMATION DISCLOSURE<br/>STATEMENT BY APPLICANT</b><br><b>( Not for submission under 37 CFR 1.99)</b> | Application Number     |                     | 10524963   | 10524963 - GAU: 1614 |
|   | Filing Date            |                     | 2005-02-18 |                      |
|   | First Named Inventor   | David William Tonge |            |                      |
|   | Art Unit               | 1614                |            |                      |
|   | Examiner Name          | Leslie A. Royds     |            |                      |
|   | Attorney Docket Number | 100815-1P US        |            |                      |

|    |  |                          |
|----|--|--------------------------|
| 1  | BRADBURY, Robert, H et al, "New Non-peptide Endothelin-A Receptor Antagonists: Synthesis, Biological Properties, and Structure-Activity Relationships of 5-(Dimethylamino)-N-pyridyl-, -N-pyrimidinyl-, -N-pyridazinyl-, and -N-pyrazinyl-1-naphthalenesulfonamides", J Med Chem, 14 May 1997, 996-1004, 40. | <input type="checkbox"/> |
| 2  | BROOKS N. et al, "ZD4054 – a specific endothelin-A receptor antagonist providing hope for treatment of HRPC", 4th PacRim Breast and Prostate Cancer Meeting. British Columbia, Canada, 12–16 August 2008. abstract   | <input type="checkbox"/> |
| 3  | CARDUCCI M.A. et al, "Targeting bone metastasis in prostate cancer with endothelin receptor antagonists", Clin Cancer Res, 2006, 6296s–6300s, 12.  | <input type="checkbox"/> |
| 4  | CARDUCCI, M.A. et al, "The Endothelin-A Receptor Antagonist Atrasentan (ABT-627) Delays Clinical Progression in Hormone Refractory Prostate Cancer: a Multinational, Randomized, Double-Blind, Placebo-Controlled Trial", Asco Abstracts 2001.   | <input type="checkbox"/> |
| 5  | CARRAGHER N. et al "Application of 3-dimensional (3D) in vitro invasion assays demonstrate anti-invasive activity of the specific endothelin-A (ETA) receptor-antagonist ZD4054 when combined with the novel Src/Abl inhibitor AZD0530"NCRI. Birmingham, UK, 5–8 October 2008; abst B77.                     | <input type="checkbox"/> |
| 6  | CHIAO, J.W. et al, "Endothelin-1 from Prostate Cancer Cells is enhanced by bone contact which blocks osteoclastic bone resorption", British Journal of Cancer, 2000, 360-365, 83(3).   | <input type="checkbox"/> |
| 7  | CHIRGWIN, J.M. et al, "Tumor-bone cellular interactions in skeletal metastases", J Musculoskel Neuron Interact, 2004, 308-318, 4(3).   | <input type="checkbox"/> |
| 8  | CLARKSON-JONES J. et al, "Metabolism of [14C]-ZD4054 in healthy volunteers", Drug Metab Rev, 2008, 206, 40 (Suppl 3) (Abstract 283).   | <input type="checkbox"/> |
| 9  | CLARKSON-JONES J. et al, "Metabolism of [14C]-ZD4054 in healthy volunteers", poster, ISSX – 15th North American Regional Meeting, San Diego, USA, 12–16 October 2008   | <input type="checkbox"/> |
| 10 | CURWEN J et al, "The impact of ZD4054, a specific endothelin-A receptor antagonist, on tumor blood supply, invasion and the bone microenvironment" Mol Cancer Ther, 2007;6(12) Suppl II:abst A272.   | <input type="checkbox"/> |
| 11 | CURWEN J et al, "The impact of ZD4054, a specific endothelin-A receptor antagonist, on tumor blood supply, invasion and the bone microenvironment", AACR-NCI-EORTC, San Francisco, USA, 22–26 October 2007. Poster.  | <input type="checkbox"/> |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /LAR/ (05/14/2009)

|   |                        |                     |            |                      |
|---|------------------------|---------------------|------------|----------------------|
| <b>Receipt date: 01/30/2009</b><br><br><b>INFORMATION DISCLOSURE<br/>STATEMENT BY APPLICANT</b><br><b>( Not for submission under 37 CFR 1.99)</b> | Application Number     |                     | 10524963   | 10524963 - GAU: 1614 |
|   | Filing Date            |                     | 2005-02-18 |                      |
|   | First Named Inventor   | David William Tonge |            |                      |
|   | Art Unit               | 1614                |            |                      |
|   | Examiner Name          | Leslie A. Royds     |            |                      |
|   | Attorney Docket Number | 100815-1P US        |            |                      |

|    |  |                          |
|----|--|--------------------------|
| 12 | CURWEN, J. et al, "The specific endothelin A receptor antagonist ZD4054 reduces tumour-induced angiogenesis in a preclinical model", 10th International Conference on Endothelin (ET-10). Bergamo, Italy, 16–19 September 2007; oral presentation  | <input type="checkbox"/> |
| 13 | CURWEN, J. et al, "The specific endothelin A receptor antagonist ZD4054 reduces tumour-induced angiogenesis in a preclinical model", 10th International Conference on Endothelin (ET-10). Bergamo, Italy, 16–19 September 2007; poster   | <input type="checkbox"/> |
| 14 | DAWSON N. et al, "Impact of the specific endothelin-A (ETA) receptor antagonist ZD4054 on overall survival and bone metastasis in patients with hormone-resistant prostate cancer: results of a Phase II trial", Current Treat Options Oncol 2008; 105–107, 9(Suppl 1).  | <input type="checkbox"/> |
| 15 | DAWSON N. et al, "Impact of the specific endothelin-A (ETA) receptor antagonist ZD4054 on overall survival and bone metastasis in patients with hormone-resistant prostate cancer: results of a Phase II trial", oral presentation, Chemotherapy Foundation Symposium, New York, USA, 4–7 November 2008                        | <input type="checkbox"/> |
| 16 | DAWSON N. et al, "Impact of the specific endothelin A receptor antagonist ZD4054 on overall survival and bone metastasis in patients with hormone-resistant prostate cancer: results of a Phase II trial", ASCO GU Congress, San Francisco, USA 14–16 February 2008, Genitourinary Cancers Symposium Proceedings 2008; abst 7. | <input type="checkbox"/> |
| 17 | DAWSON N. et al, "Impact of the specific endothelin A receptor antagonist ZD4054 on overall survival and bone metastasis in patients with hormone-resistant prostate cancer: results of a Phase II trial", ASCO GU Congress, San Francisco, USA 14–16 February 2008, poster.   | <input type="checkbox"/> |
| 18 | DINGEMANSE, J. et al, "Pharmacokinetics and pharmacodynamics of tezosentan, an intravenous dual endothelin receptor antagonist, following chronic infusion in healthy subjects", Br J Clin Pharmacol, 28 Apr 2002, 355-362, 53.  | <input type="checkbox"/> |
| 19 | FIZAZI K. et al, "The Effects of Endothelin-1 and Abt-627, and Endothelin-1 Antagonist, in an in Vitro Model of Bone Metastases from Prostate Cancer", Asco Abstracts 2001.  | <input type="checkbox"/> |
| 20 | GODARA G. et al, "Distinct Patterns of Endothelin Axis Expression in Primary Prostate Cancer", UROLOGY, 2007, 209-215, Vol 70(1).  | <input type="checkbox"/> |
| 21 | GODARA G. et al, "Role of Endothelin Axis in progression to Aggressive Phenotype of Prostate Adenocarcinoma", The Prostate, 2005, 27-34, 65.   | <input type="checkbox"/> |
| 22 | GROSS-GOUPIL M. et al, "Integrating Molecular Oncology into Therapeutic Strategies for Prostate Cancer", European Urology Supplements, 2009, 114–119, 8.   | <input type="checkbox"/> |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /LAR/ (05/14/2009)

/Leslie A. Royds/ (05/14/2009)

|   |                        |                     |            |                      |
|---|------------------------|---------------------|------------|----------------------|
| <b>Receipt date: 01/30/2009</b><br><br><b>INFORMATION DISCLOSURE<br/>STATEMENT BY APPLICANT</b><br><b>( Not for submission under 37 CFR 1.99)</b> | Application Number     |                     | 10524963   | 10524963 - GAU: 1614 |
|   | Filing Date            |                     | 2005-02-18 |                      |
|   | First Named Inventor   | David William Tonge |            |                      |
|   | Art Unit               | 1614                |            |                      |
|   | Examiner Name          | Leslie A. Royds     |            |                      |
|   | Attorney Docket Number | 100815-1P US        |            |                      |

|    |   |                          |
|----|---|--------------------------|
| 23 | GROWCOTT J. et al "ZD4054 – A small-molecule, specific endothelin-A receptor antagonist: providing hope for patients with hormone-resistant prostate cancer", AZ-Manchester Cancer Research Centre Showcase. Manchester, UK, 22 September 2008.   | <input type="checkbox"/> |
| 24 | GROWCOTT J. et al, "Anti-invasive activity of the specific endothelin-A receptor (ETAR) antagonist, ZD4054, in A673 rhabdomyosarcoma cells", 10th International Conference on Endothelin (ET-10). Bergamo, Italy, 16–19 September 2007. Poster.   | <input type="checkbox"/> |
| 25 | GROWCOTT J. et al, "Anti-invasive activity of the specific endothelin-A receptor (ETAR) antagonist, ZD4054, in A673 rhabdomyosarcoma cells", 10th International Conference on Endothelin (ET-10). Bergamo, Italy, 16–19 September 2007. Oral Presentation.  | <input type="checkbox"/> |
| 26 | GROWCOTT J.W. et al, "Phenotypic in vitro differentiation of the specific endothelin A receptor antagonist, ZD4054, from the selective endothelin antagonist, atrasentan", Mol Cancer Ther, 2007; 6(12) Suppl II:abst B269.   | <input type="checkbox"/> |
| 27 | GROWCOTT J.W. et al, "Phenotypic in vitro differentiation of the specific endothelin A receptor antagonist, ZD4054, from the selective endothelin antagonist, atrasentan", AACR-NCI-EORTC, San Francisco, USA, 22–26 October 2007. Poster.  | <input type="checkbox"/> |
| 28 | GROWCOTT, J.W., "Preclinical anticancer activity of the specific endothelin A receptor antagonist ZD4054", Anti-Cancer Drugs 2009, 00:000–000.  | <input type="checkbox"/> |
| 29 | GUISE T. et al, "Endothelin A Receptor Blockade Inhibits Osteoblastic Metastases", Asco Abstracts 2001.   | <input type="checkbox"/> |
| 30 | HICKINSON D.M. et al, "Enhanced in vitro anti-invasive activity in A673 rhabdomyosarcoma cells of the specific endothelin-A receptor (ETA) antagonist ZD4054 when combined with the novel Src inhibitor AZD0530", Proc Am Assoc Cancer Res, 2008, 49 :abst 1487.  | <input type="checkbox"/> |
| 31 | HICKINSON D.M. et al, "Enhanced in vitro anti-invasive activity in A673 rhabdomyosarcoma cells of the specific endothelin-A receptor (ETA) antagonist ZD4054 when combined with the novel Src inhibitor AZD0530", AACR Annual Meeting, San Diego, CA, USA, 12–16 April 2008. Poster                       | <input type="checkbox"/> |
| 32 | ISHERWOOD B. et al "Enhanced in vitro anti-invasive activity in A673 rhabdomyosarcoma cells of the specific endothelin-A (ETA) antagonist ZD4054 when combined with the novel Src/Abl inhibitor AZD0530" NCRI. Birmingham, UK, 5–8 October 2008; poster.  | <input type="checkbox"/> |
| 33 | JAMES N, et al, "The potent, specific endothelin A receptor antagonist ZD4054 improves overall survival in patients with pain-free or mildly symptomatic M1 hormone-resistant prostate cancer" 1st European Multidisciplinary Meeting on Urological Cancers. Barcelona, Spain, 2–4 November 2007;abst O2. | <input type="checkbox"/> |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /LAR/ (05/14/2009)

/Leslie A. Royds/ (05/14/2009)

|   |                        |                     |              |                      |
|---|------------------------|---------------------|--------------|----------------------|
| <b>Receipt date: 01/30/2009</b><br><br><b>INFORMATION DISCLOSURE<br/>STATEMENT BY APPLICANT</b><br><b>( Not for submission under 37 CFR 1.99)</b> | Application Number     |                     | 10524963     | 10524963 - GAU: 1614 |
|   | Filing Date            |                     | 2005-02-18   |                      |
|   | First Named Inventor   | David William Tonge |              |                      |
|   | Art Unit               |                     | 1614         |                      |
|   | Examiner Name          | Leslie A. Royds     |              |                      |
|   | Attorney Docket Number |                     | 100815-1P US |                      |

|    |  |                          |
|----|--|--------------------------|
| 34 | JAMES N. "New clinical data for the specific ETA receptor antagonist ZD4054", EAU 2008 Milan Italy, 26–29 March 2008. Oral presentation.   | <input type="checkbox"/> |
| 35 | JAMES N. et al, "The effect of ZD4054 on bone metastases in patients with M1 hormone-resistant prostate cancer as assessed by radionuclide bone scans", 1st European Multidisciplinary Meeting on Urological Cancers. Barcelona, Spain, 2–4 November 2007; abst P10.   | <input type="checkbox"/> |
| 36 | JAMES N. et al, "The effect of ZD4054 on bone metastases in patients with M1 hormone-resistant prostate cancer as assessed by radionuclide bone scans", 1st European Multidisciplinary Meeting on Urological Cancers. Barcelona, Spain, 2–4 November 2007. Poster.   | <input type="checkbox"/> |
| 37 | James N.D. et al, "ZD4054, a potent, specific endothelin A receptor antagonist, improves overall survival in pain-free or mildly symptomatic patients with hormone-resistant prostate cancer (HRPC) and bone metastases" ECCO 14, Barcelona, Spain, 23–27 September 2007. Oral Presentation.                                       | <input type="checkbox"/> |
| 38 | JAMES, N.D. et al, "Safety and Efficacy of the Specific Endothelin-A Receptor Antagonist ZD4054 in Patients with Hormone-Resistant Prostate Cancer and Bone Metastases Who Were Pain Free or Mildly Symptomatic: A Double-Blind, Placebo-Controlled, Randomised, Phase 2 Trial" Eur Urol (2008), doi:10.1016/j.eururo.2008.11.002. | <input type="checkbox"/> |
| 39 | JAMES, N.D. et al, "ZD4054, a potent, specific endothelin A receptor antagonist, improves overall survival in pain-free or mildly symptomatic patients with hormone-resistant prostate cancer (HRPC) and bone metastases", European Journal of Cancer Supplements, 2007, abstract 3LB, Vol. 5, No. 6.                              | <input type="checkbox"/> |
| 40 | KENYON A. et al, "The mystery of the co-eluting peak"; DMDG meeting. Cambridge, UK, 17–19 September 2007. Poster.  | <input type="checkbox"/> |
| 41 | KNIGHT L.J. et al, "Hypermethylation of endothelin receptor type B (EDNRB) is a frequent event in non-small cell lung cancer", Proc Am Assoc Cancer Res, 2007, 48:abst 1135.   | <input type="checkbox"/> |
| 42 | KNIGHT L.J. et al, "Hypermethylation of endothelin receptor type B (EDNRB) is a frequent event in non-small cell lung cancer", AACR, Los Angeles, CA, USA, 14–18 April 2007. Poster  | <input type="checkbox"/> |
| 43 | KNIGHT, L.J., "Epigenetic silencing of the endothelin-B receptor gene in non-small cell lung cancer", International Journal Of Oncology, 2009, 465-471, 34.  | <input type="checkbox"/> |
| 44 | KOPETZ, Scott E et al, "Endothelin-1 as a target for therapeutic intervention in prostate cancer", Investigational New Drugs, May 2002, 173-182, 20.   | <input type="checkbox"/> |

|   |                        |                     |            |                      |
|---|------------------------|---------------------|------------|----------------------|
| <b>Receipt date: 01/30/2009</b><br><br><b>INFORMATION DISCLOSURE<br/>STATEMENT BY APPLICANT</b><br><b>( Not for submission under 37 CFR 1.99)</b> | Application Number     |                     | 10524963   | 10524963 - GAU: 1614 |
|   | Filing Date            |                     | 2005-02-18 |                      |
|   | First Named Inventor   | David William Tonge |            |                      |
|   | Art Unit               | 1614                |            |                      |
|   | Examiner Name          | Leslie A. Royds     |            |                      |
|   | Attorney Docket Number | 100815-1P US        |            |                      |

|    |  |                          |
|----|--|--------------------------|
| 45 | MOHAMMAD K., et al, "Combined endothelin A receptor antagonist and bisphosphonate treatment more effectively reduces prostate cancer growth in bone than either alone", American Society for Bone and Mineral Research, 27th Annual Meeting. 2005; 1213a.  | <input type="checkbox"/> |
| 46 | NELSON J.B.et al, "Endothelin-1 inhibits apoptosis in prostate cancer", Neoplasia 2005, 631-7, 7(7) (abstract).  | <input type="checkbox"/> |
| 47 | NELSON J.B.et al, "The Endothelin Axis: Emerging Role In Cancer", Nature Reviews Cancer, 2003, 110-116, 3.   | <input type="checkbox"/> |
| 48 | NELSON J.B.et al, "The Endothelin-A Receptor Antagonist Atrasentan (ABT-627) Reduces Skeletal Remodeling Activity in Men with Advance Refractory Prostate Cancer", Asco Abstracts 2001.  | <input type="checkbox"/> |
| 49 | PAYNE H. et al, "Progression-free survival, overall survival and bone metastasis in a phase II trial of the specific endothelin a receptor antagonist ZD4054 in patients with hormone-resistant prostate cancer", CURy congress. Barcelona, Spain, 31 January – 3 February 2008. oral presentation | <input type="checkbox"/> |
| 50 | PFLUG BR et al, "Defining the basis of an operational model for enhanced efficacy of combination therapy using an endothelin receptor antagonist and chemotherapeutic agents", Mol Cancer Ther, 2007;6(12) Suppl II:abst A287.   | <input type="checkbox"/> |

If you wish to add additional non-patent literature document citation information please click the Add button

#### EXAMINER SIGNATURE

|                    |                                |                 |  |
|--------------------|--------------------------------|-----------------|--|
| Examiner Signature | /Leslie A. Royds/ (05/14/2009) | Date Considered |  |
|--------------------|--------------------------------|-----------------|--|

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> See Kind Codes of USPTO Patent Documents at [www.USPTO.GOV](http://www.USPTO.GOV) or MPEP 901.04. <sup>2</sup> Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>3</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>4</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. <sup>5</sup> Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /LAR/ (05/14/2009)